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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	5

DATE MAILED: 01/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/929,819	Emanuele et al
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 5, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Aug 14, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An information disclosure statement was received and entered as Paper No. 4 on 3/5/02.

Claims 1-16 are pending and under consideration in this Office Action.

Priority

1. Applicant has claimed priority under 35 USC 120 to a variety of US patent applications. This priority claim cannot be granted for the following reasons. All instant claims embrace compositions comprising a nucleic acid and a copolymer of polyethylene oxide (POE) and polypropylene oxide (POP) polymers, wherein the copolymer is organized such that POP polymers flank a central POE polymer. However none of the priority documents provides support for this combination of limitations. For this reason, the filing date of the instant claims must be the filing date of the instant application, 8/14/01.

Claim Objections

2. Claims 6 and 14 are objected to because they are ungrammatical. The article "an" in the phrase "an low molecular weight alcohol" should be replaced with the article "a".

Compliance with Sequence Rules

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **At page 34, line 27 the specification discloses an oligonucleotide that is longer than 10 bases in length but which is not identified by a SEQ ID NO, and Applicant has not provided a Sequence Listing in either a computer readable form or on paper.**

Applicant must provide:

An initial computer readable form (CRF) copy of the "Sequence Listing".

An initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

4. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic methods and compositions capable of altering nucleic acid function as disclosed in the prior art, does not reasonably provide enablement for therapeutic compositions and methods that rely one the use of nucleic acids to alter the function of other nucleic acids as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Nature of the Invention

5. Claims 1-8 are drawn to therapeutic compositions for treating animals. The compositions must comprise a compound capable of altering nucleic acid function, and a POP-POE-POP copolymer. Claims 9 and 13-16 are drawn to methods of delivering to animals compositions comprising compounds capable of altering nucleic acid function and a POP-POE-POP copolymer.

Claims 10 and 11 are drawn to compositions intended to be delivered to an animal. Although claims 9-16 do not recite therapy, the specification discloses no purpose for these methods other than therapy.

Breadth of the Claims

6. The claims are not limited in terms of the diseases or disorders which can be treated with the compositions or methods. All claims embrace the use of nucleic acids as the compounds which can alter nucleic acid function. In other words, the claims embrace compositions and methods of delivering nucleic acids, i.e. genes, oligonucleotides, antisense oligonucleotides, triplex DNA compounds, or ribozymes, for the intended purpose of therapeutically altering nucleic acid function in vivo. The specification also teaches that the claimed compositions and methods can be used for genetic immunization. The claims do not limit the animal which can be immunized, or the diseases against which immunization is therapeutic.

Background

7. Prior to the time of the invention it was well known in the art that POP-POE-POP copolymers with the characteristics required by the instant claims could be used to deliver non-nucleic acid therapeutic molecules in vivo. See rejections under 35 USC 102 and 103 below. For example, Balasubramanian et al (US Patent 5,824,322, issued 10/20/1998) compositions and methods for increasing an immune response in an animal, wherein the compositions comprised POP-POE-POP copolymers of the instant invention (see claims 1-8). An increased immune response is deemed to be a process in which the function of nucleic acids is altered as required by

the claims, i.e. by increasing the expression of genes involved in the immune response. Kabanov et al (US Patent 6,093,391, issued 7/25/2000) taught therapeutic compositions comprising POP-POE-POP copolymers and biological agents, wherein the agent can be any of a variety of peptides and proteins including cytokines, hormones, TPA, etc. See e.g. claim 2, especially lines 29 and 30; and claim 11. Kabanov also taught that the biological agent could be a nucleic acid, but provided no evidence of a therapeutic effect. On the other hand, Abe et al (Biochem. Biophys. Res. Comm. 198(1): 16-24, 1/1994) taught the use of a POE-POP copolymer in the in vivo delivery of an antisense cdc2 oligonucleotide to reduce restenosis in a rat model. Thus, while the use of POP-POE-POP copolymers to deliver non-nucleic acid therapeutic molecules was established in the prior art, the use of these copolymers for gene therapy was not routine at that time.

State of the Art\ and Predictability of the Art.

8. In fact, at the time the invention was made, successful implementation of gene therapy protocols in general was not routinely obtainable by those skilled in the art. For example, Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor

delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph.

9. The state of the art with respect to antisense therapies is set forth by Crook (In Basic Principles of Antisense Therapeutics, Springer-Verlag, Eds, New York, pgs. 1 and 4), who teaches that although antisense techniques have progressed rapidly, "the technology remains in its infancy", and the utility of the approach is still debatable (pg. 1, Introduction). Crook points out several factors which may influence the biological effect of an antisense oligonucleotide (AODN), including the rate of uptake of the AODN, rate of distribution within the target cell, stability within the target cell, local concentration of the oligonucleotide, and the concentration and stability of the target mRNA (pgs. 1 and 4). Furthermore, Branch (Trends in Biochem Sci 23: 45-50, 1998) teaches that selection of appropriate antisense sequences is difficult because secondary structures of mRNAs *in vivo* frequently restrict access of antisense oligonucleotides to the target sequence (page 45, col. 3. first para., page 48, last para. and page 49). Branch states,

"Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49, col. 2, last para.).

10. The state of the art of genetic immunization was set forth by McCluskie et al (Molecular Medicine 5(5): 287-300, 1999). McCluskie considers the effects of the routes of administration of DNA vaccines on the quality of any resulting immune response, and considers the relevance of animal models to practice in humans. Pertinent to the instant case, McCluskie teaches that "promising results in animal models have not been realized in human trials and considerable effort is now being focused at understanding this difference and developing ways of improving the efficacy of DNA vaccines." See final sentence of first paragraph on page 288, column 1. McCluskie points out that "[t]he strength and nature of immune responses in mice with DNA vaccines appear to be influenced by a number of factors [citation omitted]; however, these variables may not be of similar importance in larger animals including humans. As such, optimization methods developed in mice may not necessarily be applicable to humans." See page 288, column 2, first full paragraph. In fact, it is clear that some vaccines developed in mice do not function at all in some primates. At page 296, column 2, second full paragraph, McCluskie states that "[t]he realization that results in mice often do not predict the situation in humans also led to a large number of DNA vaccine studies in non-human primates, including Aotus monkeys, rhesus monkeys, and chimpanzees. IM injection of plasmid DNA vaccines, while highly immunogenic in mice was found to be only relatively so in chimpanzees and essentially not at all in Aotus monkeys. Furthermore, although early human studies have demonstrated the safety and potential

of DNA vaccines, results obtained have not been as good as predicted from animal models. Collectively, these results indicate that no animal model may be ideal for prediction of efficacy in humans [citations omitted]."

11. McCluskie concludes "[i]n summary, mice may have limited value for choosing the best route of DNA vaccine delivery for humans. While efficacy in murine models has preceded the successful development of many human vaccines, it is probably safe to say that any vaccines that work in a human will work in a mouse, but not necessarily *vice versa*. Therefore it is difficult to predict from mouse studies the potential of a new vaccine in humans. In fact, in those human trials that have been carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors. Furthermore, although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement to first transfect cells and express antigens, relies on many factors other than immunological responses to the antigen. We will not know the answer to this until after greater experience has been achieved in non-human primates and human clinical trials." See paragraph bridging pages 296 and 297.

12. One might argue that the results of Abe, discussed above, regarding the successful treatment of restenosis in a rat carotid artery model are evidence of the enablement of the instant invention with regard to gene therapy. However, the prior art teaches that successful application of restenosis treatments in small animal models is not predictive of success in other animals,

particularly in humans. Muller et al (J. Amer. Coll. Cardiol. 19(2):418-432, 1992) teach that, as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in response to arterial injury in animal models. However, none of these agents reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. To explain these results, Muller considered the differences between the various systems. Significant interspecies and intraspecies differences were found to exist among the various animal models, particularly with respect to the extent and composition of neointimal thickening, drug and lipid metabolism, and the activity of coagulation and fibrinolytic systems. Muller teaches that these differences may account for the variability in sensitivity of various animal models to treatments, and should be considered carefully in the interpretation of experimental studies. See abstract. Reilly et al (Drug Dev. Res. 29(2): 137-147, 1993) teach that the angioplasty procedure performed in the rat model used in the instant invention differs from the procedure applied in humans. Reilly teaches that in humans, angioplasty is performed on preexisting lesions in the coronary artery, whereas it is performed on normal carotid arteries, with lower shear forces and exposure times, in the rat model. Furthermore, Reilly considers that the mechanical and elastic properties of the two artery types may differ. Pertinent to this issue, Muller points out that there are fundamental physiological differences between rat and human arteries, particularly with respect to the amount of elastin. See page 420, paragraph bridging columns 1 and 2; and page 421, column 1, lines 4-8. Lafont et al (Card. Res. 39(1): 50-59, 7/1998) substantiate the teachings of Reilly, and expand on the reasons that rat restenosis model is

deficient. Lafont reiterates that the rat model uses a normal, not a diseased artery, and does not reflect human angioplasty because it utilizes a type of balloon which stretches the artery in a different way than an angioplasty balloon. Lafont also teaches that the resulting lesion is histologically unlike human atherosclerosis because it lacks calcification and calcium deposits, and because it occurs in an otherwise normal artery. See page 52, lines 3-12. In conclusion, Lafont indicates that while animal models may be useful for determining the mechanism of a drug on smooth muscle cell proliferation, positive results should not be interpreted to mean that a given treatment will function in humans. "The extrapolation of animal studies directly to man is unreasonable given the vast differences between animal models and man, and the complexity of the restenotic process." See page 54, column 2, lines 3-12. Further evidence of the unpredictability of extrapolating results from animal studies of smooth muscle cell proliferation inhibition comes from Lafont et al (Ann. Card. Ang. 44(7): 349-353, 9/1995), who review the results of fifteen years of research prior to 1995. Lafont concludes that "[a]ll the restenosis strategies based on inhibition of smooth muscle cell proliferation, which successfully limited restenosis in animal models have failed in man, due to hazardous extrapolations from experimental models which are very different from the atheromatous lesions observed in man". See abstract. In fact, the unpredictability in extrapolating results of such studies to humans was noted as late as 1999, when Johnson et al (Thromb. Haemost 81:835-843, 1999) taught that small animal models "lacked efficiency in predicting the success of interventions to inhibit restenosis in humans", and

found that small animal models fail to closely simulate human atherosclerosis and stenotic lesions. See abstract.

Level of Skill of Those in the Art

13. In summary, it is clear from the foregoing that although there were scattered reports of success in the general fields of gene therapy, antisense therapy, and genetic immunization, at the time the invention was filed these fields were highly unpredictable, and even those of the highest level of skill in the biotechnological art could not perform these methods in a general sense, as is instantly claimed, with routine success.

Guidance and Examples in the Specification

14. The specification teaches no working examples of gene or antisense therapy. A single example of the induction of an immune response in a mouse by administration of a block copolymer and a nucleic acid encoding a viral antigen is given at page 37, lines 15-27. However, the specification fails to disclose the nature of the copolymer used in the procedure, so it is not clear that the structural and functional characteristics of the copolymer used are the same as those of the copolymers recite in the instant claims. Further, there is was no apparent protective or therapeutic effect disclosed. The specification provides no guidance for improving the state of the art of in vivo gene expression, oligonucleotide design, or genetic immunization such that one of skill in the art could overcome the art-recognized unpredictability in these methods as summarized above.

Amount of Experimentation Required to Practice the Invention

15. In view of the state of the art of nucleic acid mediated therapies, including genetic immunization, the unpredictability associated with these methods, the failure of those of skill in the art to routinely obtain success in these methods, and the failure of the specification to address the art-recognized difficulties associated with these methods, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

Written Description

16. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

17. Claims 1-16 are drawn to the genus of compounds "capable of altering nucleic acid function". As discussed above under enablement, it is clear from the specification that these compounds should be therapeutic in nature, so the claimed genus is considered to be compounds capable of altering nucleic acid function to therapeutic effect in an animal. The breadth of the claimed genus is unclear. At page 32, lines 32-35 Applicant implies that the claimed genus embraces **any and all** compounds that can alter nucleic acid function, and is not limited to only oligo- or polynucleotides. However, in view of the limitation of claims 5 and 12 to the

subgenuses of genes, oligonucleotides, antisense, triplex compounds, and ribozymes, the written description analysis will begin with a consideration of these subgenuses.

18. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species has been described by complete structure, such as nucleotide sequence, next it is determined whether a representative number of species has been described by other relevant identifying characteristic. Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov).

19. At page 34, line 27, Applicant discloses by complete structure an antisense oligonucleotide corresponding to regions of the *art/trs* genes of HIV. However it is unclear as to whether this oligonucleotide can be used to therapeutic effect because the specification discloses no working example, and because the art of oligonucleotide mediated therapy is highly unpredictable as established above under enablement. So, it is unclear whether or not this oligonucleotide is a member of the claimed genus. The specification discloses by complete structure no other oligo- or polynucleotide that can be used for therapy. The specification discloses by relevant identifying characteristic, i.e. by name, two other genes purported to be useful in therapy. The specification discloses the ADA gene and the herpes simplex virus gD gene at page 35, lines 28 and 29 and page 36, line 23, respectively. No other oligo-or polynucleotides are disclosed by any relevant identifying characteristic. There is no evidence of record that either of these genes can be used to therapeutic effect.

20. The question now arises as to whether or not this disclosure constitutes a description of a representative number of species. The Guidelines on Written Description indicate that what constitutes a representative number of species varies inversely with the skill and knowledge in the art, and that in an unpredictable art such as gene therapy, adequate written description of a genus cannot be achieved by disclosing only one species within the genus. In this case, it is not clear that the specification has disclosed any single species that is representative of any of one the subgenuses set forth in claims 5 and 12, therefore one of skill in the art could not conclude that applicant was in possession of the claimed invention at the time of filing.

21. In consideration of the broader claims embracing any and all compounds that alter gene function, clearly the specification fails to satisfy the written description requirement because it fails to adequately describe the subgenuses set forth in claims 5 and 12. Furthermore, while the specification discloses a list of antibiotics and antivirals at page 14, lines 20-33, this cannot serve as an adequate description of the subgenus comprising non-nucleic acid compounds, because this subgenus includes drugs that are totally unrelated to antibiotics and antivirals such as cytokines, immunosuppressants, hormones, growth factors, and any other drug that has any effect, direct, or indirect, on gene expression. The specification does not describe such compounds by reduction to practice, complete structure, relevant identifying characteristics, or by any other means set forth in the Written Description Guidelines. For these reasons one of skill in the art could not conclude that Applicant was in possession of the claimed invention at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

23. Claims 1-16 are indefinite because they recite "human" and "animal" as alternatives. This is confusing because humans are animals. Deletion of the word "human" is suggested.

24. These claims also recite "the compound" without proper antecedent basis. For example, claim 1 lines 18 and 19 recite "about 40% of the compound by weight", in apparent reference to the POE portion of the copolymer. Similarly lines 22 and 23 of claim 1 recite "about 90% of the compound by weight". These passages appear to refer to the octablock copolymer, but the only antecedent for "the compound" is "a compound capable of altering nucleic acid function admixed with a block copolymer" in lines 5 and 6.

25. Claims 4 and 12 are incomprehensible. For the purposes of consideration under 35 USC 102 and 103, these claims were read as if the phrase "the mean aggregate molecular weight of the portion of the wherein" had been deleted.

26. Claims 5 and 13 are indefinite because the metes and bounds of the word "genes" are unclear. The specification fails to define the term, and there is no single art-recognized definition. For example, the term is regularly used to refer only to a coding sequence (open reading frame), but is also regularly used to refer to a genetic unit comprising 5' and 3' noncoding sequences, and

introns as well. It is unclear which definition Applicant intends, so it is unclear what are the metes and bounds of the claims.

27. Claims 14 and 15 are confusing because the purpose in the method of further including a surfactant and an alcohol is unclear. The claims fail to recite at what step the surfactant and alcohol should be added, or to what composition they should be added. Claims 7 and 15 are indefinite because they contain the trademark/trade name "Tween 80". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material of product, the claim does not comply with the requirements of 35 USC 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be properly used to identify any particular material or product. A trademark or trade name is used to identify a source of goods, not the goods themselves. Thus a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case the trademark or trade name is used to identify or describe polyoxyethylene sorbitan monooleate and, accordingly, the identification or description is indefinite. See MPEP 2173.05(u).

28. Claim 16 is confusing because the purpose in the method of further including an expression vector is unclear. The claims fail to recite at what step the expression vector should be added, or to what composition it should be added.

Claim Rejections - 35 USC § 102

29. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

30. Claims 1-5 and 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Kabanov et al (US Patent 6,093,391, issued 7/25/00).

31. Kabanov teaches compositions comprising POP-POE-POP copolymers and biological agents, wherein the agent can be any of a variety of peptides and proteins including cytokines, hormones, TPA, etc. See e.g. claim 2, especially lines 29 and 30; and claim 11. Kabanov also teaches methods of treatment. See claims 15-27. Kabanov teaches at least two copolymers (25R1 and 31R1) that meet the limitations for hydrophobe molecular weight and percentage 2500, 90 3100, 90 hydrophile required by any of the instant claims. See column 14, lines 26 and 30.

Thus Kabanov anticipates the claims.

32. Claims 1-4 and 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Balasubramanian (US Patent 5,824,322, issued 10/20/98).

33. Balasubramanian teaches compositions and methods for increasing an immune response in an animal, wherein the compositions comprise POP-POE-POP copolymers of the instant invention and an antigen (see claims 1-8).

34. Claims 1-3 and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Jansen et al (US Patent 4,902,500).

35. Jansen teaches methods of stabilizing antibodies in octablock copolymers, and administering the antibodies to animals. For example, Jansen taught that POP-POE-POP polymers having a molecular weight between 950 and 4000 and a POE content up to about 80% could be used to deliver antibodies in vivo for therapeutic purposes (see column 1, line 65; column 2, lines 21-24 33-37; and column 2, line 63 to column 3, line 9.

Thus Jansen anticipates the claims.

36. Claims 1-5, 8-13 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Lemieux et al (US Patent 6,359,054, issued 3/19/02).

37. Lemieux teaches methods of delivering to a patient a composition comprising POP-POE-POP block copolymers and nucleic acids, (see e.g. claim 13 at column 49). The nucleic acid can be an expression vector, antisense, ribozyme, or oligonucleotide (see column 21, lines 15-29).

The POP-POE-POP block copolymers useful in the invention include 22R4, 25R1, 25R2, 25R4, 25R5, 31R1, 31R2, and 31R4 (see column 14, lines 34-36 and 54-62). Each of these copolymers meets the limitations of claims 1-3, 5, 8-11, 13, and 16 regarding the composition and organization of the copolymer. Copolymers 25R1 and 31R1 meet the limitations of claims 4 and 12 regarding the composition and organization of the copolymer.

Thus Lemieux anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

38. Claims 4 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jansen et al (US Patent 4,902,500).

39. Jansen teaches methods of stabilizing antibodies in octablock copolymers, and administering the antibodies to animals. For example, Jansen taught that POP-POE-POP copolymers having a molecular weight between 950 and 4000 and a POE content up to about 80% could be used to deliver antibodies in vivo for therapeutic purposes (see column 1, line 65; column 2, lines 21-24 33-37; and column 2, line 63 to column 3, line 9.

40. Jansen does not teach a composition in which the POE content is approximately 10% as required by claims 4 and 12.

41. It would have been obvious to one of ordinary skill in the art to arrive at POP-POE-POP copolymer having approximately 10% POE content through the process of routine optimization. Jansen teaches copolymers having "up to approximately 80%" POE content. This can be construed as 0-80%, thereby embracing the claimed limitation of "approximately 10%". Thus Jansen teaches the general conditions of the claims. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

Thus the invention as a whole was *prima facie* obvious.

42. Claims 5 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kabanov et al US Patent 6,093,391, issued 7/25/00) in view of Kabanov et al (US Patent 5,656,611, issued 8/12/97).

43. Kabanov '391 teaches compositions comprising POP-POE-POP copolymers and biological agents, wherein the agent can be a nucleic acid or a polynucleotide. See e.g. column 6, lines 27-34, and claim 2, especially lines 29 and 30. Kabanov teaches at least two copolymers (25R1 and 31R1) that meet the limitations for hydrophobe molecular weight and percentage hydrophile required by any of the instant claims. See column 14, lines 26 and 30.

44. Kabanov '391 does not explicitly teach that the nucleic acids or polynucleotides may be expression vectors, oligonucleotides, antisense oligonucleotides, ribozymes, triplex DNA compounds or genes.

45. Kabanov '611 teaches compositions comprising antisense, oligonucleotides, ribozymes, or expression vectors (see column 10, lines 9-28) and POP-POE-POP copolymers. See abstract and column 7, line 23 to column 8, line 11, especially column 7, lines 35-38).

46. Given the suggestion of Kabanov '391 to use POP-POE-POP copolymers to deliver nucleic acids and polynucleotides, it would have been obvious to one of ordinary skill in the art at the time of the invention to use these copolymers to deliver the antisense, oligonucleotides, ribozymes, or expression vectors of Kabanov '611. One would have been motivated to do so because it was routine in the prior art at the time of the invention to use copolymers composed of POE and POP for this purpose as shown by the teachings of Kabanov '611.

Thus the invention as a whole was *prima facie* obvious. 44.

47. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kabanov et al US Patent 6,093,391, issued 7/25/00) and Kabanov et al (US Patent 5,656,611, issued 8/12/97) as applied to claims 5 and 8 above, and further in view of Abe et al (Biochem. Biophys. Res. Comm. 198(1): 16-24, 1/1994).

48. The teachings of Kabanov '391 and Kabanov '611 are summarized above and render obvious compositions comprising antisense oligonucleotides and POP-POE-POP copolymers

such as Pluronics 25R1 and 31R1 that meet the limitations for hydrophobe molecular weight and percentage hydrophile required by the claim.

49. These references do not enable a method of delivering the entire scope of these composition in vivo.

50. Abe et al teach the use of a POE-POP copolymer in the in vivo delivery of antisense oligonucleotides.

51. Given the teachings of Kabanov '391 and Kabanov '611 to use POP-POE-POP copolymers to deliver antisense polynucleotides, it would have been obvious to one of ordinary skill in the art at the time of the invention to use these copolymers to deliver the antisense oligonucleotides of Abe in vivo. One would have been motivated to do so in order to study restenosis in the rat model of Abe, and could have done so with a reasonable expectation of success in view of the suggestion of Kabanov '391 to use Pluronics 25R1 and 31R1 to deliver nucleic acids to cells, and the similarity of the composition of Abe.

Thus the invention as a whole was *prima facie* obvious.

Summary

Claims 1-16 are indefinite

Claims 1-16 lack adequate written description and enablement.

Claims 1-5, 8-13 and 16 are anticipated and/or obvious.

Claims 6, 7, and 14, and 15 are free of the prior art of record because the prior art doesn ot teach the combination of a POP-POE-POP copolymer, 0.1% to 5% by weight of a surfactant, and 0.5% to 5% by volume of a low molecular weight alcohol.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JEFFREY SIEW
PRIMARY EXAMINER
1/13/03